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(54) Title: METHOD FOR INCREASING OPTIC NERVE, CHOROIDAL AND RETINAL BLOOD FLOW TO FACILITATE THE PRESERVATION OF SIGHT

(57) Abstract: A method for improving visual function and maximizing the health of the optic nerve and retina by increasing blood flow velocity therein through the application of an effective amount of a formulation of an agent that increases levels of cyclic-GMP, increases levels of nitric oxide or inhibits phosphodiesterase.

DESCRIPTION

METHOD FOR INCREASING OPTIC NERVE, CHOROIDAL AND RETINAL BLOOD FLOW TO FACILITATE THE PRESERVATION OF SIGHT

BACKGROUND OF THE INVENTION

The present application claims priority to provisional application serial number 60/148,150 filed August 10, 1999. The entire text of the above–referenced disclosure is specifically incorporated by reference herein without disclaimer.

1. Field of the Invention

The present invention relates generally to the field of ocular medicine. More particularly, it concerns methods for treating ocular disorders and for maintaining ocular health. The present invention relates more specifically to a method for improving visual function and optimizing the health of the optic nerve and retina by increasing blood flow therein through the application of an effective amount of a composition including an agent that increases cyclic-guanosine monophosphate (cyclic-GMP) levels, either directly, or by stimulating cyclic-GMP synthesis, or by inhibiting cyclic-GMP selective phosphodiesterase(s).

2. Background Information

The vision process in general involves a complex pathway into the brain. To see, light must enter through the cornea and the lens; penetrate the back of the eye through the retina; pass the ganglion cells and bipolar cells; then pass down to the outer plexiform layers through the synaptic vesicle, the inner fiber, the nucleus, the outer fibers, the terminal bars, the cilium; and finally reach the photoreceptors, which can be considered to carry out the instant film processing of the visual light beam. After the light beam has been processed in the photoreceptor disks, it passes back through the cilium, the ellipsoid, myoid, Mueller cells, outer fiber, nucleus, inner fiber, synaptic vesicle, the outer plexiform layer, inner nuclear layer, the bipolar cells, the inner plexiform layer,

finally reaching the ganglion cells where it is processed into an axon signal. After it reaches the ganglion cells, the signal is transported through the optic nerve fibers to the brain where it is assessed and compounded by the visual brain lobes to form the visual picture. It is believed that the uninterrupted signal carried by the retina, the optic nerve head, and the optic nerve fibers is the most crucial part of the process for creating the visual picture. Adequate blood flow nurtures the tissues along this path and, therefore, assures axonal flow.

It is understood that the human eye (and indeed the eye structure of most mammals) has two largely independent circulatory systems, retinal and uveal. Retinal circulation accounts for only about 2% of total eye circulation, but this 2% is critical to the health of the eye's neural connection to the brain, *i.e.*, the 1.2 million axons which make up the nerve trunk known as the optic nerve. The cell bodies containing the genetic material and metabolic machinery for this connection are all located in the inner layer of the retina, and derive virtually all of their blood supply (*i.e.*, including energy, oxygen/carbon dioxide, and metabolic by-product exchange) from the locally auto-regulated retinal circulation. Any significant compromise to the retinal circulation is typically accompanied by visual loss.

The vast majority of the eye's inner circulation, on the other hand, passes through the uveal system, a sponge-like, erectile tangle of vessels that lies behind the retina and its pigment epithelium. This vascular bed provides a rich supply of nutrients to the metabolically active photoreceptors of the outer retina, and the pigment epithelium which supports them. Moreover, this seemingly excessive blood supply acts as a heat sink to absorb thermal energy from focused light which could otherwise damage neural tissues. The choroidal circulation, the part of the uveal vascular bed lying directly behind the retina, has some local regulation characteristics, but is also supplied with autonomic nerves capable of producing major changes in circulatory volume in response to stimuli, not necessarily generated in the eye itself.

To address retinal and optic nerve blood flow velocity, it is important to understand that the retina is essentially a specialized part of the brain, and its circulation

is very tightly regulated. Blood flow through the brain is typically constant in healthy individuals, whether running a marathon or sleeping. Obviously, huge variations in the inflow pressure of carotid artery blood to the brain occur throughout a typical day, and the vasculature in the cerebral cortex responds by adjusting its resistance. This is accomplished by constriction or dilation of the vessels throughout the brain. If the cerebrospinal fluid pressure is increased, creating, in effect, a stiffer vascular bed in the cerebral cortex, the blood vessels in the brain dilate to reduce intrinsic resistance, maintaining constant blood flow. This process is called autoregulation.

Autoregulation in the retina is analogous to that found in the brain, so if intraocular pressure is reduced, circulation in the retina is not necessarily increased. This point is clearly illustrated as a coincidental feature of the examples of hyperventilation (to blow off carbon dioxide and thereby reduce circulation to all the intrinsic vessels of the eye) and treatment with latanoprost (increasing the flow of clear fluid out of the eye), which both produce significant reduction of intraocular pressure, but with which visual function may actually be simultaneously diminished.

Circulation in the retina also is highly pH-dependent. Studies in which various gases are introduced via the respiratory system into the blood stream clearly demonstrate that as the CO_2 level increases and pH decreases, circulation to the retina typically increases by upward of 40% from the baseline level observed during breathing of atmospheric air. Conversely, breathing pure oxygen produces a profound decrease in circulation in the retina. This latter response may be in part responsible for the disease process known as retrolental fibroplasia, or retinopathy of prematurity, which causes total or partial blindness in many premature infants.

In healthy eyes, because of the choroid's relative abundance of vessels, fairly large changes in choroidal blood flow may be accompanied by minimal visual function change. However, because the uveal circulation comprises a significant portion of the ocular volume, a substantial drop in choroidal blood flow is generally accompanied by a significant decrease in intraocular pressure. Thus, during hyperventilation for example, when the natural vasodilator carbon dioxide is blown off, both choroidal and retinal

circulation decrease in tandem, and visual function diminishes correspondingly. Typically, an individual with a large intraocular pressure decrease consequent to hyperventilation would have a very large visual function deficit.

It has, therefore, become increasingly apparent that blood flow in the retina and about the optic nerve plays a critical role in a number of ocular disorders. New technologies have facilitated a more thorough examination of the posterior aspect of the eye and the evaluation of circulatory, metabolic, and hematologic factors, thereby being better able to determine the causes of various eye diseases. In turn, various therapeutic agents may be applied to more precisely address the pathophysiology underlying specific ocular disorders, more particularly, those ocular disorders whose progression may be attenuated, ameliorated, or reversed by improving ocular circulation.

For example, others have used drugs to stimulate cyclic 3', 5'-adenosine monophosphate (cAMP) production, thereby decreasing intraocular pressure and increasing ocular circulation. It is well known that beta-adrenergic impulses in several tissues are mediated intracellularly by a second messenger, cAMP. cAMP is produced from ATP by a membrane bound enzyme, adenylate cyclase. cAMP is believed further to activate steps in a chain of processes leading to protein phosphorylation and final biologic activity. Generally, it is thought that the cAMP step is a process of short duration because cAMP is rapidly and efficiently degraded intracellularly by cAMP phosphodiesterases, which are present in abundance.

The pathway by which cAMP is produced is quite complex. cAMP is produced when adenylate cyclase is activated through the activation of many receptors. This stimulation is mediated by G_s and by inhibition of at least one other protein belonging to the G_i class of G proteins. It is known that there are at least ten tissue-specific adenylate cyclase isozymes, each having a unique pattern of regulatory responses. Some of these isozymes are inhibited by G protein $\beta\gamma$ subunits, others are stimulated by these subunits if concurrently stimulated by the α subunit of G_s, others are stimulated by Ca^{2+} or Ca^{2+}-calmodulin complexes. Adrenergic drugs mediate the production of cAMP, thereby decreasing intraocular pressure and increasing vascular blood flow.

In general, diseases which may be amenable to treatment with agents capable of modulating ocular blood flow include, but are not limited to, optic nerve disease, retinal disease or choroidal disease. More specific disorders include, but are not limited to, macular edema or macular degeneration. Macular edema, for example, is defined as swelling within the retina in the critically important central visual zone at the posterior pole of the eye. An accumulation of fluid tends to distract the retinal neural elements from one another and from their local blood supply, creating a dormancy of visual function in the area. Usually, the process is self-limiting, but occasional permanent visual disability results from macular edema. Often times, the swelling may take many months to clear. The precise mechanism by which swelling is triggered is uncertain, but it is probable that certain natural metabolic toxins may play an important role in the disease process. Macular swelling also may follow the insertion of artificial lens implants and cataract surgery, particularly if there is a breach in the lens capsule which segregates the vitreous gel from the fluid-filled anterior chamber. Longstanding macular edema after cataract surgery is one of the most frustrating dilemmas in all of ophthalmology, and is remarkably common. Macular edema is a common and alarming ocular problem, for which no useful form of ocular therapy has been previously known. Two types of cystoid macular edema are: (a) those without vascular leakage: retinitis pigmentosa and other pigmentary retinal degenerative disorders, early stage macular hole, and choroidal neovascularization; and (b) those with vascular leakage: diabetic retinopathy; branch retinal vein occlusion; intermediate uveitis; and ideopathic retinal telangiectasis.

Another even more common chronic condition is macular degeneration. Instead of fluid accumulating in the outer retina, hard accumulations of lipofuscin, a metabolic waste product, tend to accumulate between the photoreceptors and the villi of the retinal pigment epithelium. These accumulations gradually enlarge, and in their early pathologic phase create discrete accumulations known as drusen. The lipofuscin is believed to accumulate as a result of the breaking off of the photoreceptor elements. Shedding of the cellular components of the photoreceptors is constantly occurring in a healthy retina. Good retinal pigment epithelial metabolism generally ensures a rapid clearance of such

catabolic by-products of vision. The accumulation of this waste material retards the interaction between the retina and the retinal pigment epithelium from which nutrients arrive and through which catabolites are cleansed, establishing a self-perpetuating cycle of catabolite accumulation. The accumulations not only block metabolic transfer between the retina and retinal pigment epithelium, they actually continue to undergo photoresponsive metabolism, constantly wasting precious NADH reducing power with no benefit.

Improved local circulation might retard or prevent the accumulation of lipofuscin and break the cycle of progressive blockage and waste of metabolic products passing to and from the retina. As drusen accumulate in number and begin to coalesce, vast areas of retinal photoreceptors may become permanently disengaged from their neighboring retinal pigment epithelial villi. The sections of retina so affected become blind. Unfortunately, the greatest propensity among the aging population is for drusen to accumulate in the very central area of vision, the macula. Thus, macular degeneration is the most common cause of legal blindness in the United States and Europe. Whereas macular edema generally affects only one eye, macular degeneration typically involves both eyes and is usually fairly symmetric in its presentation and progression. The problem is on the rise, and is expected to continue to mount.

Obviously, normal metabolism tends to produce catabolic waste with accumulation of protons and CO_2. Many chronic diseases of the ocular tissues tend to stagnate local metabolism and the normal catabolites which would otherwise 'recruit' increased local circulation, are actually not produced. Instead, tissue breakdown products accumulate producing a vicious cycle of degredation without replenishment. Thus, a variety of agents capable of enhancing local circulation in this situation could help clear tissue breakdown products and stimulate a restoration of normal metabolic function.

SUMMARY OF THE INVENTION

The present invention provides a method for treating an optic nerve disease by increasing ocular blood flow, perfusion and/or circulation. Ocular blood flow is

generally improved by applying a pharmacologically effective amount of an agent that enhances ocular vascular blood flow either directly to the eye or systemically. As used herein, the phrase "agent that enhances ocular vascular blood flow" refers to cyclic-GMP analogs, agents that inhibit cyclic-GMP phosphodiesterase(s) (PDE), agents that increase the activity of guanylate cyclase, agents that increase levels of cyclic-GMP, or agents that increase levels of nitric oxide (NO) in the tissues of the eye. For example, agents that either enhance the production or increase the availability or longevity of NO, thereby activating guanylate cyclase, would increase levels of cyclic-GMP and cause an increase in ocular blood flow.

In preferred embodiments, the optic nerve disease to be treated includes but are not limited to normotensive excavatory optic neuropathy, ischemic optic neuropathy, toxic optic neuropathy, traumatic optic neuropathy, or idiopathic optic neuropathy. Examples of normotensive excavatory optic neuropathy include primary optic atrophy, ocular ischemic syndrome, shock-associated optic atrophy or chronic systemic hypotension. Examples of ischemic optic neuropathy include anterior ischemic optic neuropathy, posterior ischemic optic neuropathy, giant cell arteritis, or Foster-Kennedy syndrome. Examples of toxic optic neuropathy include drug induced optic neuropathy or nutritional optic neuropathy. Examples of traumatic optic neuropathy include inflammatory optic neuropathy or neuroretinitis. Examples of idiopathic optic neuropathy include optic nerve drusen or benign intracranial hypertension. In certain aspects of the present invention, multiple optical nerve diseases occurring in the same patient are treated using the compositions and methods of the invention.

Alternatively, the invention provides methods for treating retinal disease by administering a composition comprising an agent that enhances ocular vascular blood flow to a patient suffering from a retinal disease or applying the composition directly to the affected eye. In certain aspects, the retinal disease to be treated may be retinal neovascularization, ischemic hematologic/rheologic disorders or toxic maculopathy. Examples of retinal neovascularization include a diabetes related form of retinal neovascularization, hemoglobinopathy or inflammatory vascular narrowing. The diabetes related form of retinal neovascularization is may be, for example, diabetic

macular edema, ischemia and neovascularization or non-proliferative diabetic retinopathy. An example of hemoglobinopahy is sickle cell trait. Examples of inflammatory vascular narrowing include lupus, collagen vascular diseases, HIV retinopathy, CMV retinopathy or sarcoidosis. Examples of ischemic hemotologic/ rheologic disorder include central retinal vein occlusion or branch retinal vein occlusion. Examples of toxic maculopathy include drug related maculopathy or chloroquine retinopathy. In certain aspects of the present invention, multiple retinal diseases occurring in the same patient are treated using the compositions and methods of the invention.

In certain other preferred methods of the invention, choroidal disease is treated by applying a therapeutically effective amount of a composition comprising at least a first agent that increases ocular blood flow to an affected eye. Examples of choroidal disease include, but are not limited to, an ischemic disorder of the posterior choroid, degenerative subretinal neovascularization, diabetic choroidal ischemia, inflammatory subretinal neovascularization, or non-age related choroidal ischemia. Examples of ischemic disorder of the posterior choroid include degenerative drusen of the macula (*i.e.* dry age related macular degeneration), macular retinal pigment epithelial atrophy, and retinal pigment epithelial detachment. An example of degenerative subretinal neovascularization is wet age related macular degeneration. Examples of diabetic choroidal ischemia include diabetic choroidopathy. Examples of inflammatory subretinal neovascularization include presumed ocular histoplasmosis syndrome. Examples of non-age related choroidal ischemia include myopic degeneration or high myopia. In certain aspects of the present invention, multiple choroidal diseases occurring in the same patient are treated using the compositions and methods of the invention.

Of course, patients often present with multiple forms of any of the above diseases and the compositions and methods described herein are effective for treatment of multiple disorders in the same patient. For example, the compositions and methods described herein are useful for treating a patient suffering from an optical nerve disease and a retinal disease.

The methods of the invention are further effective for the treatment of macular disorders such as macular edema, macular degeneration, drusen, macular disorders related to hypertension, angioma, papillitis, neuroretinitis or pigmentary retinal degenerative disorders, toxic maculopathy and maculopathy secondary to rheologic abnormalities. The methods of the invention are useful for treatment of macular edema with or without vascular leakage. Examples of macular edema without vascular leakage include retinitis pigmentosa, pigmentary retinal degenerative disorder, early stage macular hole, or choroidal neovascularization. Examples of macular edema with vascular leakage include diabetic retinopathy, branch retinal vein occlusion, intermediate uveitis or ideopathic retinal telangiectasis. The methods of the invention may also be used to inhibit or prevent the accumulation of lipofuscin in an eye.

In the methods of the invention described above, the agent to be included in the composition is a cyclic-GMP analog, a compound that inhibits cyclic-GMP PDE(s), a compound that activates guanylate cyclase, or a compound that increases levels of cyclic-GMP. Preferred cyclic-GMP analogs include 8-bromoguanosine-3,5-cyclic monophosphate. Preferred agents that inhibit cyclic-GMP PDE(s) include sildenafil citrate, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, or zardaverine, carboline derivatives, pyridocarbazole derivatives, or quinozolinone compounds. In certain preferred aspects, the PDE inhibitor is selective for PDE type 5 (PDE5) or PDE type 6 (PDE6). Preferred agents that activate guanylate cyclase (by increasing levels of NO) include sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines. By activating guanylate cyclase, these agents also increase levels of cyclic-GMP. NO levels may also be increased by NO donors or NO synthase stimulators and such compounds are useful in the compositions for use in the methods of the invention. Preferred NO donors include sodium nitroprusside, nitroglycerine, SIN-1, isosorbide mononitrate, isosorbide dinitrate, diethylenetriamine/NO, glycerol trinitrite, pentaerytrityl tetranitrite, mannitol hexanitrite, inositol hexanitrite or propatyl nitrate. Preferred NO synthase stimulators include 2-aryl-β-thiophens. Other preferred compounds include nitrosated and/or nitroxylated PDE inhibitors or polymeric material that releases NO. Combinations of two or more of the agents listed above are also contemplated in certain aspects of the present invention.

Preferred methods of application include oral and parenteral (including ophthalmic, transdermal, pulmonary, nasal, buccal or sublingual). More specifically, the compositions may be administered by way of a solution, gel, semisolid, suspension, metered dose device, transdermal patch or film.

Another aspect of the invention provides a kit for treatment of ocular disorders including a sealed container housing a composition comprising an agent that increases ocular vascular blood flow and instructions for administering the composition to a patient suffering from an ocular disorder such that the patient's ocular blood flow is increased. The compositions included in the kit of the invention include agents as described above.

The present invention also provides an effective treatment for maintaining the health of the eye and effectively treating various other ocular conditions by improving ocular blood flow in the retina and choroid of the eye and in and about the optical nerve.

In addition to the indications above, the present invention contemplates administration of the compositions described herein to subjects with normal vision for the purpose of increasing visual function including but not limited to visual acuity, contrast sensitivity and perimetric light sensitivity.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1A is a graph of retinal blood flow as measured by Heidelberg Retinal Flowmetry (HRF) for three test subjects over time.

FIG. 1B is a graph of retinal blood velocity as measured by Heidelberg Retinal Flowmetry (HRF) for three test subjects over time.

FIG. 2A is a graph of 4.26 SF cpd contrast sensitivity (visual function) for two test subjects over time.

FIG. 2B is a graph of 8.53 SF cpd contrast sensitivity (central macular visual function) for two test subjects over time.

FIG. 3A provides Humphrey Frequency Doubling Technology (FDT) visual field reports for a first test subject baseline (left) and post-application (right) conditions.

FIG. 3B provides Humphrey Frequency Doubling Technology (FDT) visual field reports for a second test subject baseline (left) and post-application (right) conditions.

FIG. 4A is a graph of pulsatile ocular blood flow (OBF) for two test subjects over time.

FIG. 4B is a graph of intraocular pressure measured concomitantly with OBF for two test subjects over time.

FIG. 5A is a graph of blue field density (perimacular retinal capillary circulatory volume) for two test subjects over time.

FIG. 5B is a graph of blue field mean velocity (perimacular retinal capillary circulatory speed) for two test subjects over time.

FIG. 6A Humphrey visual field tests, showing extent of the perpetual progression of field loss despite maintaining intraocular pressures (IOP) from 6-10 mmHg without medication. Pericentral thresholds clockwise from superionasal were 26, 26, 14, and 25 dB.

FIG. 6B Clockwise progression of pericentral threshold values was 28, 29, 23, and 26 dB, a mean increase of 3.75 decibels for the macular region loci, nearly a tenfold increase in light sensitivity.

FIG. 7A Humphrey 10-2 visual field test, prior to and one hour after ingestion of 50 mg oral sildenafil.

FIG. 7B Humphrey visual field test showing visual thresholds of 26, 28, and 27 decibels across the central six degrees above the horizontal meridian, and 16 of the 17 superotemporal loci now had positive thresholds, 15 of which were in double-digits.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

1. Enhanced Blood flow For Treatment of Ocular Disorders

Surprisingly, agents that enhance blood flow to and around the optic nerve have been found to be useful in treating a number of eye disorders. It is known that relatively large changes in choroidal blood flow may be accompanied by minimal visual function change. However, retinal circulation is very tightly regulated within the brain. The majority of the eye's inner circulation passes through the uveal system, lying behind the retina and its pigment epithelium. Choroidal circulation is part of the vascular bed lying directly behind the retina and contains autonomic nerves capable of producing major changes in circulatory volume in response to stimuli, which may be generated within the eye or outside of the eye.

While the vision process is quite complex, it is believed that the signal carried by the retina, the optic nerve head, and the optic nerve fibers is the most crucial part of the process. Adequate blood flow nurtures the tissue along this path and assures transport of the signal. Many ocular disorders are known to involve some kind of blockage of or hindrance to optic blood flow.

The human choroid, which supports the metabolic function of the outer retina, is an erectile tissue, analogous in certain respects to the corpus cavernosum. The fenestrated choroidal vasculature is highly responsive to both local and neurogenic stimuli, and the uveal system of which it is part may hold up to 98% of the intraocular blood volume. Choroidal blood flow has recently been reported to be decreased in macular degeneration, the leading cause of acquired blindness in North America. The inventor reasoned that agents capable of modulating ocular blood flow would be of therapeutic value in the treatment of a range of choroidal, retinal, and axonal disorders, provided circulatory augmentation can be achieved without debilitating metabolic compromise or vascular leakage.

There are a number of ocular disease states in which increasing ocular blood flow is beneficial. The methods of the invention include administering agents that increase ocular blood flow to a patient suffering from such an ocular disease state. Table 1 sets forth a number of the disease states that would benefit from treatment using the methods of the present invention.

Table 1: Disease States Which Could Benefit From Increased Blood flow (Circulation) Of The Eye

General Categories	Disease Examples	More Specific Examples
Optic Nerve Disease		
Normotensive Excavatory Optic Neuropathy	Primary Optic Atrophy, Ocular Ischemic Syndrome	Shock-Associated Optic Atrophy, Chronic System Hypotension
Ischemic Optic Neuropathy	Anterior Ischemic Optic Neuropathy Posterior Ischemic Optic Neuropathy	Giant Cell Arteritis, Foster-Kennedy Syndrome
Toxic Optic Neuropathy	Drug Inducted Optic Neuropathy	Nutritional Optic Neuropathy
Traumatic Optic Neuropathy		
Inflammatory Optic Neuropathy	Neuroretinitis	
Idiopathic Optic Neuropathy		Optic Nerve Drusen, Benign Intracranial Hypertension
Retina Disease		
Retinal Neovascularization	Diabetes	Diabetic Macular Edema, Ischemia and Neovascularization, Non-Proliferative Diabetic Retinopathy
	Hemoglobinopathies	Sickle Cell Trait, etc.
	Inflammatory Vascular Narrowing	Lupus, Collagen Vascular Diseases, HIV Retinopathy, CMV Retinopathy, Sarcoidosis
Ischemic Hematologic/Rheologic Disorders	Central Retinal Vein Occulsion, Branch Retinal Vein Occulsion	
Toxic Maculopathy	Drug Related Maculopathy	Chloroquine Retinopathy
Choroidal Disease		
Ischemic Disorders of the Posterior Choroid	Degenerative Drusen of the Macula, Macular Retinal Pigment Epithelial Atrophy, Retinal Pigment Epithelial Detachment	
Degenerative Subretinal Neovascularization	Age Related Macular Degeneration "Wet"	
Diabetic Choroidal Ischemia	Diabetic Choroidopathy	
Inflammatory Subretinal Neovacularization	Presumed Ocular Histoplasmosis Syndrome	
Non-Age Related Choroidal Ischemia	Myopic Degeneration	High Myopia (Greater than 7 diopters)

As illustrated in Table 1 (not intended to be exhaustive), there are generally three broad categories of optic disease states for which increased ocular blood flow is beneficial. Those are optic nerve disease, retina disease and choroidal disease. Within those general categories are a number of additional categories with more specific examples provided for illustration. Of course, those skilled in the art would understand that other disease states in which ocular blood flow is a factor would benefit from treatment using the methods of the invention. The benefits of the present invention are described in more detail below using a specific type of choroidal disease, age related macular degeneration, for illustration purposes only. It will be understood that the present methods and compositions are useful for the treatment of any optic disease state.

Age-related macular degeneration (ARMD) is the leading cause of visual loss among Americans over 60 years of age. As the macula degenerates, central reading vision deteriorates while peripheral vision is rarely affected. There are two forms of ARMD, dry or atrophic ARMD, and wet or exudative ARMD. Wet ARMD is associated with abnormal blood vessel growth (subretinal neovascularization) and accounts for a high proportion of the most severe visual destruction encountered among ARMD patients. Wet ARMD, however, only accounts for 10% of ARMD cases. Because of its dramatic pathologic course, wet ARMD has received much attention, and numerous treatment modalities have been devised to abate this form of the disease, most of which are directed toward destroying the invading, leaky blood vessels by laser or other means. Dry ARMD is far more prevalent, progresses more slowly, and accounts for 90% of ARMD cases. Advanced cases of dry ARMD constitute a high proportion of individuals declared legally blind in the United States, Europe, Australia, and parts of Asia. In addition, a high proportion of wet ARMD cases begin as dry ARMD. Despite the long-felt need for effective treatments for dry ARMD, none were available prior to the present invention.

The circulation of blood through vessels underlying the retina, in the choroid, is compromised in patients afflicted with ARMD (Pauleikboff *et al.* 1990; Chen *et al.* 1990; Giovannini *et al.* 1994; Grunwald *et al.* 1994; Friedman *et al.* 1995; Ross *et al.*

1998; Ciulla *et al.* 1999; Dontsov *et al.* 1999). Because the choroid provides the only source of nourishment for the photoreceptors in the outer retina, and the only means for removing waste products, this decrease in circulation can have dire effects on the macula, one of the body's most metabolically active tissues.

In ARMD, accumulation of lipofuscin, an aggregate of breakdown products from the outer retina, occurs in the interspace between the retinal photoreceptors and the villiform pigment epithelial cells with which they interdigitate. The retinal pigment epithelium (RPE) is a vital metabolic factory, which reprocesses photopigment and carries out many critical support and transport processes, maintaining retinal function. The outermost layer of the anatomic sandwich supporting retinal function is the choroid, a highly vascular tissue which supplies nutrients to and which clears catabolites from this highly active tissue complex. Lipofuscin builds up in the interface between the RPE and choroid in diseased eyes. Incompletely-degraded, lipofuscin-bound pigmentary debris which accumulates in this space in ARMD constantly seizes and oxidatively wastes molecular energy passing from the choroid to the RPE, even in the absence of light (Sponsel *et al.* 2000). Therefore, ARMD, once established, tends to follow a vicious pathologic spiral, selectively afflicting the zone of highest metabolic activity, the macula.

Other major sources of blindness, wet ARMD, myopic degeneration, or diabetic retinopathy, are characterized by the formation of abnormal vessels behind or within the substance of the retina. The new, abnormal vessels which typify these conditions proliferate through the action of locally-released hormonal agents, which are released in response to attenuated circulation within the eye. Such vessels, even after they form, are only sustained by persisting circulatory inadequacy in the surrounding tissue. Normalization of the balance between metabolic tissue demand, nutrient provision, and catabolite clearance results in the regression of these leaky and potentially blinding anomalous vessels. Therefore, the present methods and compositions that increase blood flow in the retina and choroid are expected to be of benefit in treating the latter stages of wet ARMD and proliferative diabetic retinopathy. In addition, timely treatment of at-risk individuals with preproliferative diabetes and dry ARMD, as described herein, is expected to prevent progression to the neovascular stages of these diseases.

2. Agents That Enhance Blood flow

The present invention is grounded on the discovery that increasing ocular blood flow, particularly in the retina of the eye is a safe and effective way to maintain the health of the eye and to treat various ocular disorders that have in their etiology inadequate vascular blood flow, such as macular edema and macular degeneration. While the precise theory is not completely understood, improved (*i.e.*, increased) blood flow in and to the retina and choroid of the eye can greatly improve retinal and optic nerve health which, in turn, effectively combats macular edema, macular degeneration, and other ocular disorders.

It is known that the enzyme guanylate cyclase catalyzes the conversion of guanidine triphosphate (GTP) to cyclic-GMP. When guanylate cyclase is activated, cyclic-GMP levels increase. Murad *et al.* used nitrogen containing compounds, such as sodium azide, sodium nitrite and hydroxylamine, to activate guanylate cyclase and discovered that these compounds are converted to an active intermediate, nitric oxide (NO), that is directly involved in the activation of guanylate cyclase and the subsequent conversion of GTP to cyclic-GMP. Thus, agents that activate guanylate cyclase through the formation of the intermediate NO, thereby increasing NO levels and, subsequently, increasing cyclic-GMP levels, and increasing ocular vascular blood flow, are particularly useful in the methods of the present invention. The compositions of the invention may include more than one agent that activates guanylate cyclase.

As mentioned above, cyclic-AMP is also known to increase vascular blood flow, however, it operates through a significantly different pathway than that of cyclic-GMP. In short, certain adrenergic drugs mediate the production of cyclic-AMP, thereby decreasing intraocular pressure and increasing vascular blood flow. Therefore, this mechanism of action is significantly different from the pathway followed by cyclic-GMP in the stimulation of ocular vascular blood flow as described herein.

Besides the agents that activate guanylate cyclase, such as sodium azide, sodium nitrite, or hydroxylamine, discussed above, other agents that activate guanylate cyclase, increase NO levels and/or increase cyclic-GMP levels also would increase ocular blood flow and improve vision. Other guanylate cyclase activators include hydrazines, nitroglycerine, nitroprusside, nitrosureas and nitrosamines.

Agents that increase NO levels include those agents that are nitric oxide donors, stimulate nitric oxide synthase or increase availability or longevity of nitric oxide. Agents that stimulate nitric oxide synthase include 2-aryl-β-thiophens, described for example, in U.S. Patent No. 5,811,437, incorporated herein by reference or other compounds described, for example, in U.S. Patent No. 5,478,946, incorporated herein by reference. Agents that are nitric oxide donors include sodium nitroprusside, nitroglycerine, SIN-1, isosorbide mononitrate, isosorbide dinitrate, diethylenetriamine/NO, glycerol trinitrite, petnaerytrityl tetranitrite, mannitol hexanitrite, inositol hexanitrite, or propatyl nitrate. Other compounds useful in the compositions of the invention include nitrosated and/or nitrosylated PDE inhibitors (as described, for example, in U.S. Patent Nos. 5,958,926 and 5,874,437, each incorporated herein by reference), or polymeric material that releases NO (as described, for example, in U.S. Patent Nos. 5,994,444 and 5,770,645, each incorporated herein by reference). The compositions of the invention may include more than one agent that increases NO levels.

It is also known that inhibition of cyclic-GMP PDE(s), especially inhibition of PDE type 5 and type 6, promotes an increase in levels of cyclic-GMP (cGMP), which in turn fosters an increase in blood flow in the uveal system. This is characterized by increased blood flow velocity in the retina and the tissue surrounding the optic nerve. Thus, agents that inhibit cyclic-GMP PDE(s) also are useful in the methods of the present invention. The compositions of the invention may include more than one inhibitor of cyclic-GMP PDE(s).

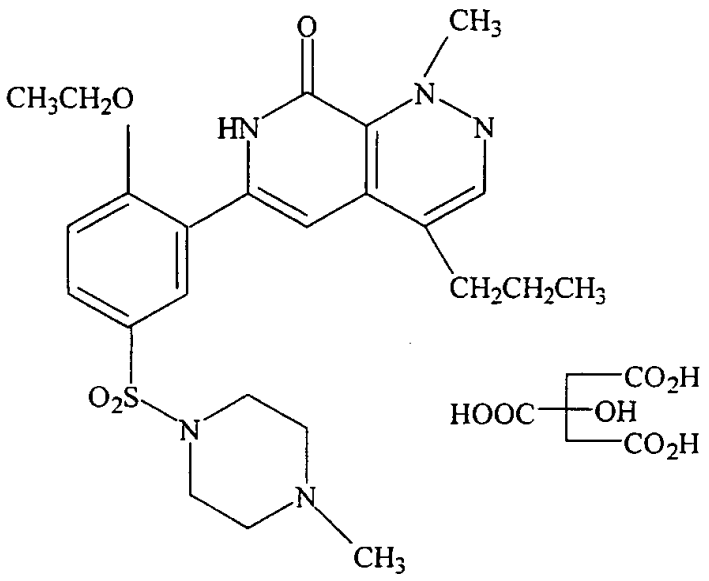
Zaprinast and dipyridamole are both known to be inhibitors of the type 5 PDE family and would, therefore, be expected to act to increase ocular blood flow in the

methods of the present invention. Other PDE inhibitors useful in the methods of the invention include filaminast, denbufyllene, piclimalist, pentoxyfilline, carboline derivatives (as described, for example, in U.S. Patent No. 6,043,252, incorporated herein by reference), pyridocarbazole derivatives (as described, for example, in U.S. Patent No. 6,018,046, incorporated herein by reference) or quinozolinone compounds (as described, for example, in U.S. Patent No. 6,087,368, incorporated herein by reference).

It will also be understood that the compositions of the invention may include a combination of any of the above described agents.

The following more detailed discussion of a particular preferred compound for use in the methods of the present invention is provided for illustration purposes only and is not meant to limit the scope of the invention. Those skilled in the art will recognize that agents described above, and other agents that act similarly, are useful in the methods of the invention.

A particularly preferred compound for use in accordance with the present invention is sildenafil (preferably the citrate salt). Sildenafil is known to cause smooth muscle relaxation and an increase in blood flow, and is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific PDE type 5 (PDE5). Sildenafil citrate is designated chemically as 1-[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7. Sildenafil citrate has most recently been utilized as the basis for an oral therapy for erectile dysfunction and has been marketed by Pfizer Labs under the trademark Viagra®. Publications relating to benign visual side-effects (e.g., blue-shift in vision, light-sensitivity, and blurring noted to occur in some patients) of sildenafil prompted the FDA to insist on product insert warnings.

In spite of these side effects, the inventor hypothesized that sildenafil might be therapeutically beneficial in an appropriate setting. Elevation of cyclic-GMP levels, a potent vasodilator, is brought about by the effect of sildenafil on PDE activity. Appreciating this mechanism (*i.e.*, the local effects of the PDE inhibitor on intracellular cyclic-GMP), and possible centrally-mediated neurogenic effects, the inventor reasoned that sildenafil could conceivably mediate significant increases in choroidal blood flow. Therefore, changes in vision and ocular blood flow were evaluated among a dozen clinician volunteers before and after taking a single 50 mg oral dose of sildenafil. It was revealed that both choroidal circulation and high resolution central visual function were substantially increased by oral sildenafil.

There were significant increases in pulsatile ocular blood flow (+29 percent; from 916 +/-103 to 1185 +/-158 μl/min; p≤0.02) and contrast sensitivity (+34 percent; from 92 +/-11 to 122 +/-11 log units; p≤0.01), 110 +/- 8 min after sildenafil administration. Retinal microcirculation increased in 7 of the 9 eyes in which there were stable scans (+8 percent; p≤0.09). The results of perimetry did not change significantly, nor did mean systolic and diastolic blood pressure, systemic pulse amplitude, and intraocular pressure. None of the subjects reported any subjective visual symptoms (Sponsel *et al.* 2000).

Pulsatile ocular blood flow occurs as a result of cardiac-synchronous filling of the choroidal circulation, in which the majority of the ocular blood volume is found. The increase in pulsatile choroidal blood flow after sildenafil administration was probably due to dilatation of the choroidal vessels, because there were no changes in intraocular pressure or systemic pulse amplitude, other major determinants of choroidal blood flow.

The mechanism associated with sildenafil citrate's use as a therapy for erectile dysfunction may explain its efficacious use in the methods of the present invention. The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide (NO) by inhibiting PDE type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

Studies *in vitro* (by Pfizer) have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known PDEs (>10-fold for PDE6, >80-fold for PDEl, >1,000-fold for PDE2, PDE3, and PDE4). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility.

3. Formulations for Use in Treatment of Ocular Disease States

Agents for use in the methods of the present invention may be delivered orally, parenterally, or may be formulated for direct topical application to the eye. The use of the term "applying" herein refers to any of the methods of delivery, including orally, parenterally, topically or otherwise. These delivery systems are effective to administer the compositions for use in the methods of the invention to the eye for the purpose of increasing optical nerve and retinal blood flow velocity. It will be appreciated that in accordance with the invention, the compositions can be administered by way of a solution, gel, semisolid, suspension, metered dose device, transdermal patch or film. Other means of delivery are also contemplated. The routes of administration of sildenafil citrate, for example, are typically oral and parenteral (including ophthalmic, transdermal, pulmonary, nasal, buccal, sublingual).

Preferred compositions for use in the methods of the present invention will typically, but not necessarily, comprise a solution, gel, semisolid, suspension, metered dose device, transdermal patch or film including, for example, an agent that enhances ocular blood flow, a buffer system (*e.g.*, hydrochloric acid, sodium hydroxide, boric acid, sodium borate, acetic acid, sodium acetate, sodium biphosphate, monobasic sodium phosphate, dibasic sodium phosphate, sodium carbonate, sodium acid phosphate, disodium phosphate, sodium thiosulfate; 0.1 - 5 % of each, or the like), a preservative system (*e.g.*, benzalkonium chloride 0.01 - 5%, benzethonium chloride 0.01 - 5%, chlorobutanol 0.01 - 5%, methylparaben 0.01 - 5%, propylparaben 0.01 phenylmercuric acetate 0.01 - 5%, phenylmercuric nitrate 0.01 - 5%, thimerosal 0.01 -sorbic acid 0.01 - 5%, sodium perborate 0.01 - 5%, benzyl alcohol 0.01 - 5% or the like), an absorption enhancer system (*e.g.*, polysorbate 80 0.005 - 6%, tocopherol TPGS 0.01 - 10'7c, tyloxapol 0.005 - 6%, or the like), a stabilizer system (*e.g.*, ascorbic acid 0.01 - 5%, tocopherol 0.01 - 5%, disodium ethylenediaminetetraacetate 0.01 - 5%, tetrasodium ethylenediaminetetraacetate 0.01 - 5%, or the like), a surfactant system (*e.g.*, polysorbate 80 0.005 - 6%, tyloxapol 0.005 - 6%, poloxamer 0.5 - 10%, or the like), a viscosity-increasing system (*e.g.*, polyvinyl alcohol 0.5 - 5%, polyethylene glycol 0.5 -

5%, hydroxypropyl methylcellulose 0.5 - 5%, povidone 0.5 - 5%, hydroxyethyl cellulose 0.5 - 5%, methylcellulose 0.5 - 5%, dextran 0.5 - 5%, acacia 0.5 - 5%, white petrolatum 50 - 99.9%, mineral oil 1 - 8%, lanolin I - 8%, propylene glycol 1 - 20%, glycerin 1 - 20%, carbopol 1 - 10%, carboxymethyl cellulose 0.5 - 5%, lanolin alcohols 0.5 -5%, or the like), a gelling system (*e.g.*, carbopol 1 - 10%, polyvinyl alcohol 0.5 - 5%, hydroxypropyl cellulose 0.5 - 10%, hydroxyethyl cellulose 0.5 - 10%, methyl cellulose 0.5 - 10%, poloxamer 0.5 - 10%, polyacrylamide 0.5 - 10%, hyaluroriic acid 0.5 - 10%, gellan gum 0.5 - 10%, pectin 0.5 - 10%, or the like) , an osmolality adjusting system (potassium chloride 0.2 - 0.9%, sodium chloride 0.2 - 0.9%, magnesium chloride 0.2 - 0.9%, calcium chloride 0.2 - 0.9%, zinc sulfate 0.2 - 0.9%, polyethylene glycol 0.2 - 0.9%, boric acid 0.2 - 0.9%, or the like) and a vehicle (*e.g.*, water, white petrolatum; 5 - 99.9% for each).

While some compositions for use in the present invention may include all of the above listed elements, other useful compositions may include less than all of the above listed elements, which generally serve to increase stability, storability, storage life, *etc.* For example, it is contemplated that compositions including a compound that enhances ocular blood flow, *i.e.*, by increasing NO, increasing cyclic-GMP, and/or inhibiting cGMP PDE, with a buffer system and a vehicle may be useful. Alternatively, compositions including a compound that enhances ocular blood flow, with a viscosity-increasing system and an osmolality adjusting system may be useful. These examples are intended to be illustrative of certain preferred embodiments and are not meant to be exhaustive or limiting the scope of the invention in any way.

A preferred composition contains sildenafil citrate in an oral or ophthalmic preparation such as those described above. For embodiments in which sildenafil citrate is administered orally, the sildenafil citrate will typically be present in amounts ranging from between about 5 mg to about 500 mg per dose. More preferably, the oral dose will contain from between about 10 mg to about 400 mg of sildenafil citrate, or between about 15 mg and about 300 mg of sildenafil citrate or between about 20 mg and about 250 mg of sildenafil citrate or between about 25 mg and about 200 mg of sildenafil citrate. Most preferably, the oral dose will contain about 50 to 100 mg sildenafil citrate. It will be

understood that a range, for example of between about 5 mg to about 500 mg, includes all integral amounts within the range, i.e., 6 mg, 7 mg, 8 mg, 9 mg etc., 30 mg, 31 mg, 32 mg, 33 mg, etc., 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, etc., 55 mg, 56 mg, 57 mg, 58 mg, etc., 75 mg, 76 mg, 77 mg, 78 mg, etc. 101 mg, 102 mg, 103 mg, 104 mg, etc., 150 mg, 151 mg, 152 mg, 153 mg, etc. 201 mg, 202 mg, 203 mg, 204 mg, etc, 220 mg, 221 mg, 222 mg, 223 mg, etc., 450 mg, 451 mg, 452 mg, 453 mg, etc., 475 mg, 476 mg, 477 mg, 478 mg, 479 mg, etc.

Preferred ophthalmic preparations of the present invention will generally include sildenafil citrate, for example, in concentrations of between about .001 % and about 20 % (weight per volume), including all amounts within the range. More preferably, sildenafil citrate will be present in the ophthalmic preparations in concentrations of between about .01 % and 5 % and most preferably, the ophthalmic preparations of the invention will contain about 1% sildenafil citrate. Of course, those skilled in the art will understand that the stated ranges include all amounts within the range, *i.e.*, .02 %, .03 %, .04 %, etc., .1 %, .11 %, .12 %, etc., .2 %, .3 %, etc., 1 %, 1.1 %, 1.2 %, 1.3 %, 1.4 % etc. 4.0 %, 4.1 % 4.2 %, 4.3 %, 4.4 %, 4.5 %, 4.6 %, 4.7 %, 4.8 %, 4.9 %, etc., 15 %, 16 %, 17 %, 18 %, 19 % etc.

Where desired, a convenient manner to deliver a metered dose is through the use of a device that is pressurized with a propellant system or is delivered by an aqueous pump spray. The propellant system may include 1,1,1,2-tetrafluoroethane (30 -99.9%) and/or 1,1,1,2,3,3,3-heptafluoropropane (30 - 99.9%) or other known propellants. Where employed, ethanol is typically used as a cosolvent (0.5 - 5%), although other solvents may also be useful in conjunction with the methods of the invention. The preferred median droplet size distribution for the pulmonary pressurized metered dose inhaler is 2 - 5 microns and the preferred median droplet size distribution for the nasal pressurized metered dose inhaler is 10 - 20 microns.

Exemplary processes for formulation include the following:

For the solution formulation, a quantity of an agent that enhances ocular vascular blood flow, such as sildenafil citrate (solubility of 3.5 mg/ml), is dissolved in a portion of the vehicle. The vehicle contains a cosolvent system to increase the solubility of the drug (agent that enhances ocular vascular blood flow) in the vehicle. The pH of the solution is adjusted and the solution is buffered. The solution is preserved and the tonicity is adjusted. The viscosity of the solution is adjusted by adding a viscosity-increasing agent. The final volume of the solution is adjusted using the remainder of the vehicle. The solution is packaged in an appropriate container/closure system to optimize stability of the drug substance and the integrity of the finished product.

For the gel formulation, the gelling agent is dissolved into an aliquot of water. In a separate portion of water, the drug, preservative, stabilizer, buffer and osmolality adjusting agent is dissolved. This blend is combined with the gel and stirred until homogeneous. The temperature may be elevated in order to enhance the mixing process. A high shear homogenizer is preferred to prepare the gel formulation. The drug-containing gel is packaged in an appropriate container/closure system to optimize stability of the drug substance and the integrity of the finished product.

For the semisolid formulation, the vehicle is heated using low heat and the preservatives are added to the molten vehicle mixture. The drug is then incorporated with continuous mixing into the molten vehicle mixture and homogenized at 2500 - 5000 psi. The preparation is removed from the heat source and continuously mixed until congealed at room temperature. The finished semisolid is packaged into an appropriate container/closure system to optimize the stability of the drug substance and the integrity of the finished product.

For the suspension formulation, an amount of micronized agent in excess of the solubility (for example, more than 3.5 mg/ml of sildenafil citrate) is added to an aqueous vehicle containing the surfactant system, preservative system, buffer system, osmolality adjusting agent, and a viscosity increasing system. The suspension is homogenized using a high shear mixer (5000 psi pressure) until the drug is uniformly distributed. The finished suspension containing the agent that enhance ocular vascular blood flow, is

packaged into an appropriate container/closure system to optimize the stability of the drug substance and the integrity of the finished product.

It is contemplated that the container/closure system containing the composition will be included in a kit along with instructions for administration effective to increase ocular blood flow. The instructions will typically include directions for dosage, application, frequency and other relevant information pertinent to practice of the methods of the invention.

The film formulation (for delivery to the eye, skin, buccal cavity) is prepared by hot melt extrusion, cast film method, or other methods suitable for the formation of thin films. The preferred method is to mix the agent that enhances ocular vascular blood flow, such as sildenafil citrate, with a blend of thermoplastic polymers and hot melt extruding the drug containing mass through a suitable extruder. The thickness of the film is manipulated by the components of the formulation and by the operating parameters of the extruder. The film containing the drug is cut in a suitable size for ophthalmic, buccal or transdermal application, and packaged in an appropriate container/closure system to optimize the stability of the drug substance and the integrity of the finished product.

Again, the film packaged in the container/closure system may be included in a kit along with instructions for application of the film effective to increase ocular blood flow, or treat macular disorders, etc., as contemplated by the invention. The instructions will typically include such information as location of application of the film, frequency of application, time period of application, etc. The instructions may be printed on the outside of the container/closure system housing the film or may be included in the kit separately from the film container/closure system.

For the pressurized metered dose inhaler, agent that enhances ocular vascular blood flow, such as sildenafil citrate, is mixed with ethanol, to produce a "drug concentrate" and an aliquot of the drug concentrate is dispensed into an epoxy-lined aluminum can (or lined Type I glass vial). The metering valve (20 - 150 microliter preferably) is crimped onto the neck of the can. The propellant system is filled through

the valve. The canister is mated with an actuator (oral for pulmonary; nasal for delivery to the nose; ophthalmic for delivery, to the eye). Alternatively, the agent that enhances ocular vascular blood flow, such as sildenafil citrate, is administered in a metered dose aqueous dispersion using a pump. The drug is mixed with the surfactant and water. After mixing to dissolve the drug, a viscosity increasing agent is added and the mixture stirred. A preservative system is dispersed and the mixture is stirred. The drug formulation is filled into a container (high density polyethylene) and the pump is screwed on.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

A 63 year-old man with dense pericentral visual field loss in the right eye and chronic excavatory optic neuropathy developed a new extension of his right inferiotemporal scotoma on Humphrey 30-2 SITA-standard testing, splitting fixation with a threshold of 14 decibels in the macular zone of that quadrant. The patient had undergone over a dozen prior Humphrey field tests, showing perpetual progression of field loss despite maintaining intraocular pressures (IOP) from 6-10 mmHg without medication. Pericentral thresholds clockwise from superionasal were 26, 26, 14, and 25 dB (FIG. 6A).

Shortly after performing visual field and contrast sensitivity testing, the patient took a single 50 mg oral dose of sildenafil citrate (Viagra®), and repeated these visual tests 110 minutes later. There was a dramatic resolution of the pericentral perimetric

defect, which increased in threshold from 14 to 23 decibels. The clockwise progression of pericentral threshold values was 28, 29, 23, and 26 dB, a mean increase of 3.75 decibels for the macular region loci, nearly a tenfold increase in light sensitivity (FIG. 6B).

Central retinal contrast sensitivity measurements carried out before and after sildenafil administration also showed remarkable improvement. Seven-degree sine wave patterns of 1 and 4 cycles per degree (cpd) at 15 reversals per second (NeuroScientific) were presented pre- and post-sildenafil. Three complete sets of training contrast sensitivity measurements in both eyes were carried out prior to testing. Low threshold values of 5.8 and 44.0, respectively, were obtained at 1 and 4 cpd in the eye with pericentral visual field loss (OD) before the drug was administered. Thresholds in the fellow eye were 10.0 and 92.3, respectively. 110 minutes after oral sildenafil administration, left eye measures remained fairly constant, but those in the eye with the pericentral perimetric defect (OD) increased dramatically to 31.2 and 92.3, respectively, at 1 and 4 cpd. IOP and blood pressure were unaltered.

EXAMPLE 2

Another patient, an alert, 78 year-old retired professor of vascular surgery, underwent pulsatile ocular blood flow measurements and Humphrey 10-2 visual field analyses prior to and one hour after ingestion of 50 mg oral sildenafil. In his more-diseased right eye, the entire superionasal visual field was a nonfunctional absolute scotoma, and 10 of the 17 of the superiotemporal quadrant loci also had thresholds of zero (FIG. 7A). Note the near total absence of visual function in the right superionasal visual field extending into the macular zone.

The patient's pulsatile ocular blood flow (POBF) in this eye was already fairly high, 1554 µl/min. One hour after sildenafil ingestion, his right eye POBF increased to 1975 µl/min. The superonasal quadrant, previously blind, now exhibited contiguous loci with visual thresholds of 26, 28, and 27 decibels across the central six degrees above the

horizontal meridian, and 16 of the 17 superotemporal loci now had positive thresholds, 15 of which were in double-digits (FIG. 7B).

EXAMPLE 3

Quite clearly, sildenafil citrate, even when administered orally, can positively influence blood flow and visual function for a very brief period of time. Topical application of compositions comprising the drug, yielded similar surprising results:

A 45 year-old man with normal visual function, slit lamp and fundus findings underwent Humphrey 10-2 full-threshold central visual field analysis and contrast sensitivity (seven-degree sine wave patterns of 1 and 4 cycles per degree at 15 reversals per second; NeuroScientific) testing. The subject had undergone numerous previous Humphrey field and contrast sensitivity tests, eliminating the prospect of any significant learning effect on repeat testing.

Shortly after performing baseline visual field and contrast sensitivity tests, he received in masked fashion one drop of artificial tear solution to his right eye, and one drop of sildenafil solution (sildenafil 1% (10 mg/ml in Schein artificial tear solution buffered to pH 8.0)) to his left eye. He reported no discomfort with either drop, and was unaware which eye had received which agent. He repeated visual function testing in both eyes 100 minutes after receiving the eyedrops.

There was a dramatic increase in pericentral contrast sensitivity in the eye receiving sildenafil, while the function of the placebo-treated eye remained relatively constant. Contrast sensitivity (CS) ratios to the 1 cycle per degree stimulus were 203 in the right eye and 235 in the left eye prior to treatment. The placebo-treated right eye had a CS ratio of 235 after 100 minutes, while the sildenafil-treated eye had a CS ratio of 317 ($p<0.0001$). The increase in CS ratio to the 4 cycle per degree stimulus with sildenafil was similarly impressive, with values of 194 in the placebo-treated right eye versus 581 in the sildenafil-treated left eye 100 minutes after treatment ($p<0.0001$).

Humphrey 10-2 visual fields demonstrated a similar phenomenon. Despite the left eye having a lower light sensitivity than the right prior to treatment, it displayed a significantly higher retinal light sensitivity than the right eye 100 minutes after receiving topical sildenafil. The pre-treatment mean threshold value for the 10 degree visual field in the left eye was 31.2 (+/-.19) decibels; 100 minutes after sildenafil eyedrop application this had increased to 32.7 (+/-.17) decibels ($p<0.0001$), a 70% increase. Intraocular pressures remained around 10 mmHg in both eyes and did not rise during the study interval. There were no adverse effects or significant visual symptoms elicited, and ocular appearance, pupil diameter, conjunctival and corneal appearance were symmetric and normal in both eyes.

EXAMPLE 4

FIG. 1A and FIG. 1B represent patient data from three patients showing an increase in retinal blood flow and blood velocity as measured using scanning laser doppler velocimetry. The data shows the increase over a period of time up to about 85 minutes from administration of 50 mg oral sildenafil citrate (Viagra®). FIG. 1A is a graph of retinal blood flow as measured by Heidelberg Retinal Flowmetry (HRF) for three test subjects over time. FIG. 1B is a graph of retinal blood velocity as measured by Heidelberg Retinal Flowmetry (HRF) for three test subjects over time.

EXAMPLE 5

FIG. 2A and FIG. 2B represent patient data from two patients showing an increase in contrast sensitivity over a period of time up to about 75 to 125 minutes from administration of 50 mg oral sildenafil citrate (Viagra®). FIG. 2A is a graph of 4.26 SF cpd contrast sensitivity (visual function) for two test subjects over time. FIG 2B is a graph of 8.53 SF cpd contrast sensitivity (central macular visual function) for two test subjects over time.

EXAMPLE 6

FIG. 3A and FIG. 3B show an improvement in visual field response for two separate individuals. The reports show both baseline (left side of each figure) and post-administration of 50 mg oral sildenafil citrate (Viagra®). FIG. 3A provides Humphrey Frequency Doubling Technology (FDT) visual field reports for a first test subject baseline (left) and post-application (right) conditions. FIG. 3B provides Humphrey Frequency Doubling Technology (FDT) visual field reports for a second test subject baseline (left) and post-application (right) conditions.

EXAMPLE 7

FIGS. 4A, 4B, 5A and 5B represent patient data from two patients showing other relevant ocular data over a period of time up to about 100 to 200 minutes from administration of 50 mg oral sildenafil citrate (Viagra®). Fig. 4A is a graph of pulsatile ocular blood flow for two test subjects over time. FIG. 4B is a graph of intraocular pressure measured concomitantly with OBF for two test subjects over time. Fig. 5A is a graph of blue field density (perimacular retinal capillary circulatory volume) for two test subjects over time. Fig. 5B is a graph of blue field mean velocity (perimacular retinal capillary circulatory speed) for two test subjects over time.

Although the invention has been described with reference to specific embodiments, this description is not meant to be construed in a limited sense. Various modifications of the disclosed embodiments, as well as alternative embodiments of the inventions will become apparent to persons skilled in the art upon the reference to the description of the invention.

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CLAIMS:

1. A method for treating an optic nerve disease comprising administering to a patient having said optic nerve disease a therapeutically effective amount of a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP.

2. The method of claim 1, wherein said optic nerve disease is normotensive excavatory optic neuropathy, ischemic optic neuropathy, toxic optic neuropathy, traumatic optic neuropathy, or idiopathic optic neuropathy.

3. The method of claim 1, wherein the optic nerve disease is idiopathic optic neuropathy.

4. The method of claim 3, wherein the idiopathic optic neuropathy is optic nerve drusen or benign intracranial hypertension.

5. The method of claim 1, wherein the agent is a cyclic-GMP analog, a cyclic-GMP phosphodiesterase inhibitor, or a guanylate cyclase activator.

6. The method of claim 5, wherein the agent is a cyclic-GMP phosphodiesterase inhibitor.

7. The method of claim 6, wherein the agent is sildenafil, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinozolinone compound.

8. The method of claim 5, wherein the agent is a guanylate cyclase activator.

9. The method of claim 8, wherein the agent is sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines.

10. The method of claim 8, wherein the agent increases ocular nitric oxide levels through nitric oxide donors, stimulation of nitric oxide synthase or increase of the availability or longevity of nitric oxide.

11. The method of claim 1, wherein said composition is administered to an eye of said patient.

12. The method of claim 1, wherein said composition is administered orally to said patient.

13. The method of claim 11, wherein the composition is applied in the form of an ophthalmic preparation.

14. A method of treating retinal disease comprising administering to a patient a therapeutically effective amount of a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP.

15. The method of claim 14, wherein said retinal disease is retinal neovascularization, ischemic hematologic/rheologic disorders or toxic maculopathy.

16. The method of claim 14, wherein the agent is a cyclic-GMP analog, a cyclic-GMP phosphodiesterase inhibitor, or a guanylate cyclase activator.

17. The method of claim 16, wherein the agent is a cyclic-GMP phosphodiesterase inhibitor.

18. The method of claim 17, wherein the agent is sildenafil, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinolinone compound.

19. The method of claim 16, wherein the agent is a guanylate cyclase activator.

20. The method of claim 19, wherein the agent is sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines.

21. The method of claim 19, wherein the agent increases ocular nitric oxide levels through nitric oxide donors, stimulation of nitric oxide synthase or an increase of availability or longevity of nitric oxide.

22. The method of claim 14, wherein said composition is administered to an eye of said patient.

23. The method of claim 14, wherein said composition is administered orally to said patient.

24. The method of claim 22, wherein the agent is applied in the form of an ophthalmic preparation.

25. A method of treating choroidal disease comprising applying a therapeutically effective amount of a composition comprising an agent that increases ocular blood flow by elevating cyclic-GMP levels to an affected eye.

26. The method of claim 25, wherein said choroidal disease is an ischemic disorder of the posterior choroid, degenerative subretinal neovascularization, diabetic choroidal ischemia, inflammatory subretinal neovascularization, or non-age related choroidal ischemia.

27. The method of claim 26, wherein said choroidal disease is ischemic disorder of the posterior choroid.

28. The method of claim 27 wherein said ischemic disorder of the posterior choroid is degenerative drusen of the macula, macular retinal pigment epithelial atrophy, or retinal pigment epithelial detachment.

29. The method of claim 26, wherein said choroidal disease is degenerative subretinal neovascularization.

30. The method of claim 29, wherein said degenerative subretinal neovascularization is wet age related macular degeneration.

31. The method of claim 25, wherein the agent is a cyclic-GMP analog, a cyclic-GMP phosphodiesterase inhibitor, or a guanylate cyclase activator.

32. The method of claim 31, wherein the agent is a cyclic-GMP phosphodiesterase inhibitor.

33. The method of claim 32, wherein the agent is sildenafil, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinozolinone compound.

34. The method of claim 31, wherein the agent is a guanylate cyclase activator.

35. The method of claim 34, wherein the agent is sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines.

36. The method of claim 34, wherein the agent increases ocular nitric oxide levels through nitric oxide donors, stimulation of nitric oxide synthase or increase of availability or longevity of nitric oxide.

37. The method of claim 25, wherein said composition is administered to an eye of said patient.

38. The method of claim 25, wherein said composition is administered orally to said patient.

39. The method of claim 37, wherein the composition is applied in the form of an ophthalmic preparation.

40. A method for increasing ocular blood flow comprising administering a pharmacologically effective amount of a composition comprising at least a first cyclic-GMP phosphodiesterase inhibitor to a patient suffering from a macular disorder.

41. The method of claim 40, wherein said phosphodiesterase inhibitor is selective for phosphodiesterase type 5.

42. The method of claim 40, wherein said phosphodiesterase inhibitor is sildenafil citrate, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinozolinone compound.

43. The method of claim 40, wherein said administering is by topical application, orally, or perenterally.

44. The method of claim 40, wherein said macular disorder is macular edema, macular degeneration, familial drusen, macular disorders related to hypertension, angioma, papillitis, neuroretinitis or pigmentary retinal degenerative disorders.

45. A method for treating macular edema, comprising administering a therapeutically effective amount of a composition comprising at least a first agent that increases cyclic GMP to a patient suffering from macular edema.

46. The method of claim 45, wherein said agent is a phosphodiesterase inhibitor selective for phosphodiesterase type 5.

47. The method of claim 46, wherein said agent is sildenafil citrate, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinozolinone compound.

48. The method of claim 45, wherein said macular edema is without vascular leakage.

49. The method of claim 48, wherein said macular edema is retinitis pigmentosa, pigmentary retinal degenerative disorder, early stage macular hole, or choroidal neovascularization.

50. The method of claim 45, wherein said macular edema is with vascular leakage.

51. The method of claim 50, wherein said macular edema is diabetic retinopathy, branch retinal vein occlusion, intermediate uveitis or ideopathic retinal telangiectasis.

52. The method of claim 45, wherein said composition is administered to an eye of said patient.

53. The method of claim 45, wherein said composition is administered orally to said patient.

54. The method of claim 52, wherein the composition is applied in the form of an ophthalmic preparation.

55. A method for inhibiting or preventing the accumulation of lipofuscin in an eye comprising administering a composition comprising at least a first agent that inhibits phosphodiesterase type 5 to a patient suffering from accumulation of lipofuscin in the eye.

56. The method of claim 55, wherein said phosphodiesterase type 5 inhibitor is sildenafil citrate, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinozolinone compound.

57. A method for increasing ocular blood flow comprising administering a composition comprising at least a first agent that activates guanylate cyclase to a patient having an ocular disorder.

58. The method of claim 57, wherein the agent is sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines.

59. A method for increasing ocular blood flow comprising administering a composition comprising at least a first agent that increases ocular nitric oxide levels to a patient having an ocular disorder.

60. A kit for treatment of ocular disorders comprising:

a) a sealed container housing a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP; and

b) instructions for administering said composition to a patient suffering from an ocular disorder such that the patient's ocular blood flow is increased.

61. The kit of claim 60, wherein said composition includes an agent that activates guanylate cyclase.

62. The kit of claim 61, wherein said agent is sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines.

63. The kit of claim 60, wherein said composition includes an agent that inhibits cyclic-GMP phosphodiesterase.

64. The kit of claim 63, wherein said agent is sildenafil citrate, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative, or a quinozolinone compound.

65. A pharmaceutical composition for increasing ocular blood flow, comprising at least a first compound that increases ocular levels of cyclic-GMP.

66. The composition of claim 65, wherein said composition comprises a solution, gel, semisolid, suspension, metered dose device, transdermal patch, or film.

67. The composition of claim 66, wherein said solution is an ophthalmic preparation.

68. The composition of claim 65, wherein said compound that increases ocular levels of cyclic-GMP is further defined as a cyclic-GMP phosphodiesterase inhibitor, a guanylate cyclase activator, a cyclic-GMP analog or a nitric oxide donor.

69. The composition of claim 68, wherein the cyclic-GMP phosphodiesterase inhibitor is sildenafil citrate, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative or a quinozolinone compound.

70. The composition of claim 68, wherein the nitric oxide donor is sodium azide, sodium nitrite, hydroxylamine, a hydrazine, nitroglycerine, nitroprusside, a nitrosurea or a nitrosamine.

71. The composition of claim 67, wherein the ophthalmic preparation comprises a pharmaceutically acceptable carrier and sildenafil citrate at a concentration of about .001 % to about 20 % weight per volume.

72. A method for treating optic nerve disease comprising administering to a patient with said optic nerve disease a therapeutically effective amount of sildenafil citrate.

73. A method for treating retinal disease comprising administering to a patient with said retinal disease a therapeutically effective amount of sildenafil citrate.

74. A method for treating choroidal disease comprising administering to a patient with said choroidal disease a therapeutically effective amount of sildenafil citrate.

75. A method for increasing visual function comprising administering to a patient a therapeutically effective amount of sildenafil citrate to an affected eye.

76. A method for increasing ocular blood flow comprising administering to a patient in need of increased ocular blood flow a therapeutically effective amount of sildenafil citrate.

77. A method for increasing visual function comprising administering to a patient with normal vision a pharmacologically effective amount of sildenafil citrate.

78. An ophthalmic preparation comprising a pharmaceutically acceptable carrier and sildenafil citrate at a concentration of about .001 % to about 20 % weight per volume.

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Retinal Blood Flow using Scanning Laser Doppler Velocimetry

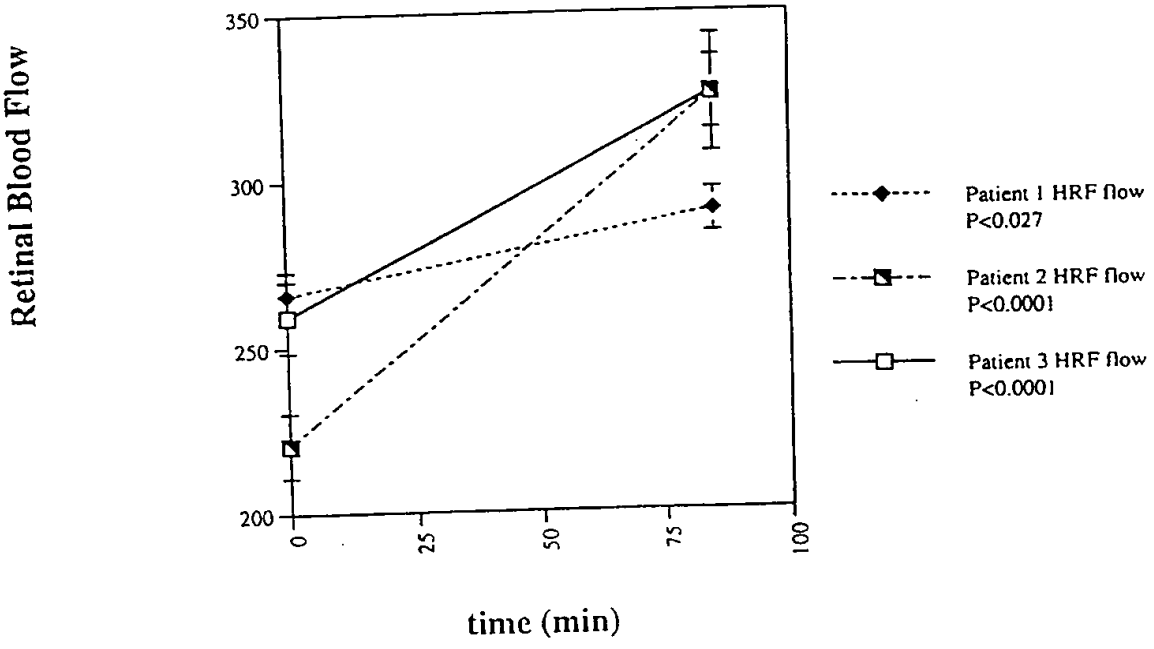


FIG. 1a

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Retinal Blood Flow using Scanning Laser Doppler Velocimetry

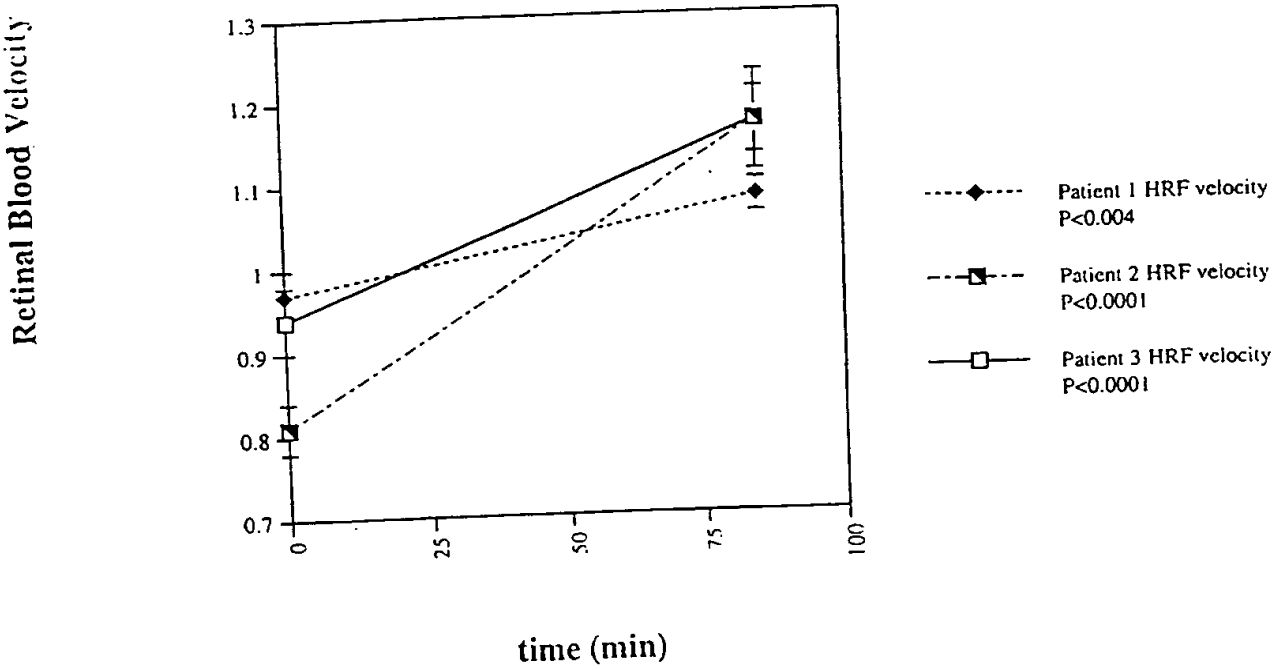


FIG. 1b

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Contrast Sensitivity

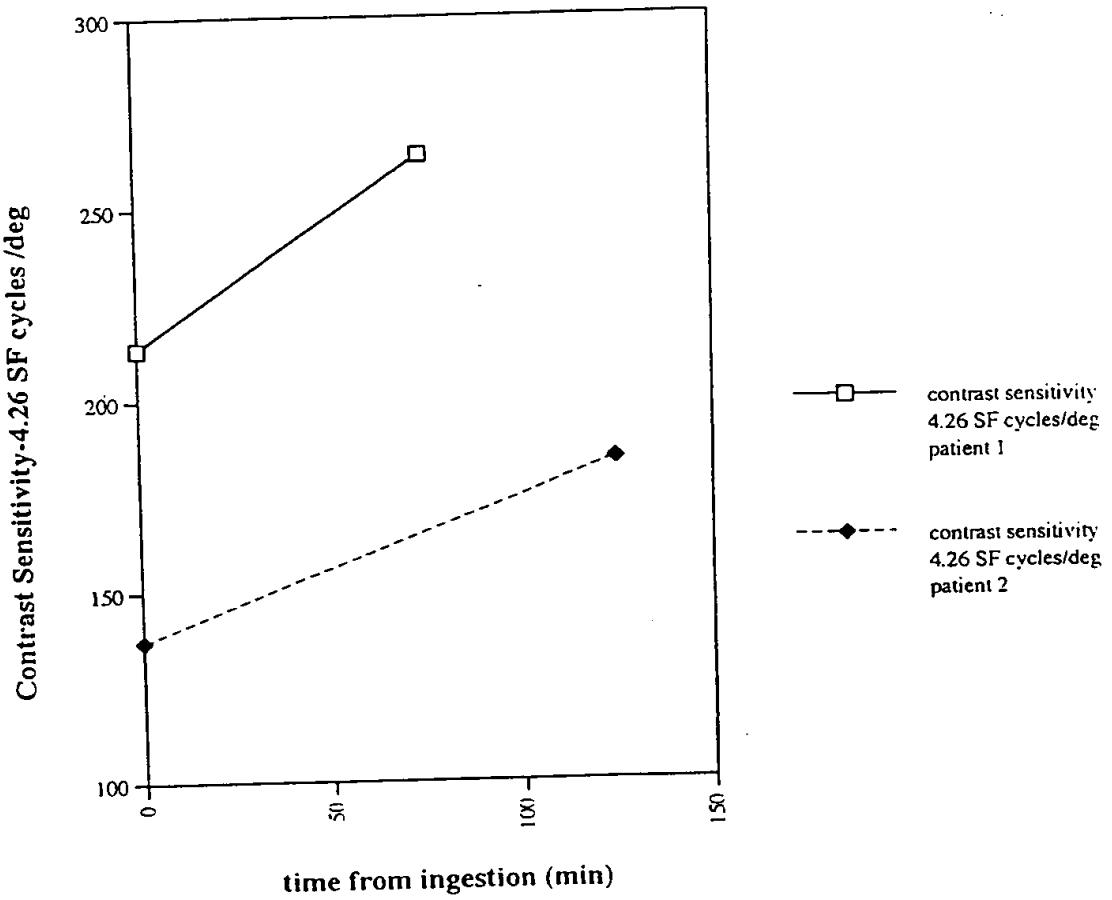


FIG. 2a

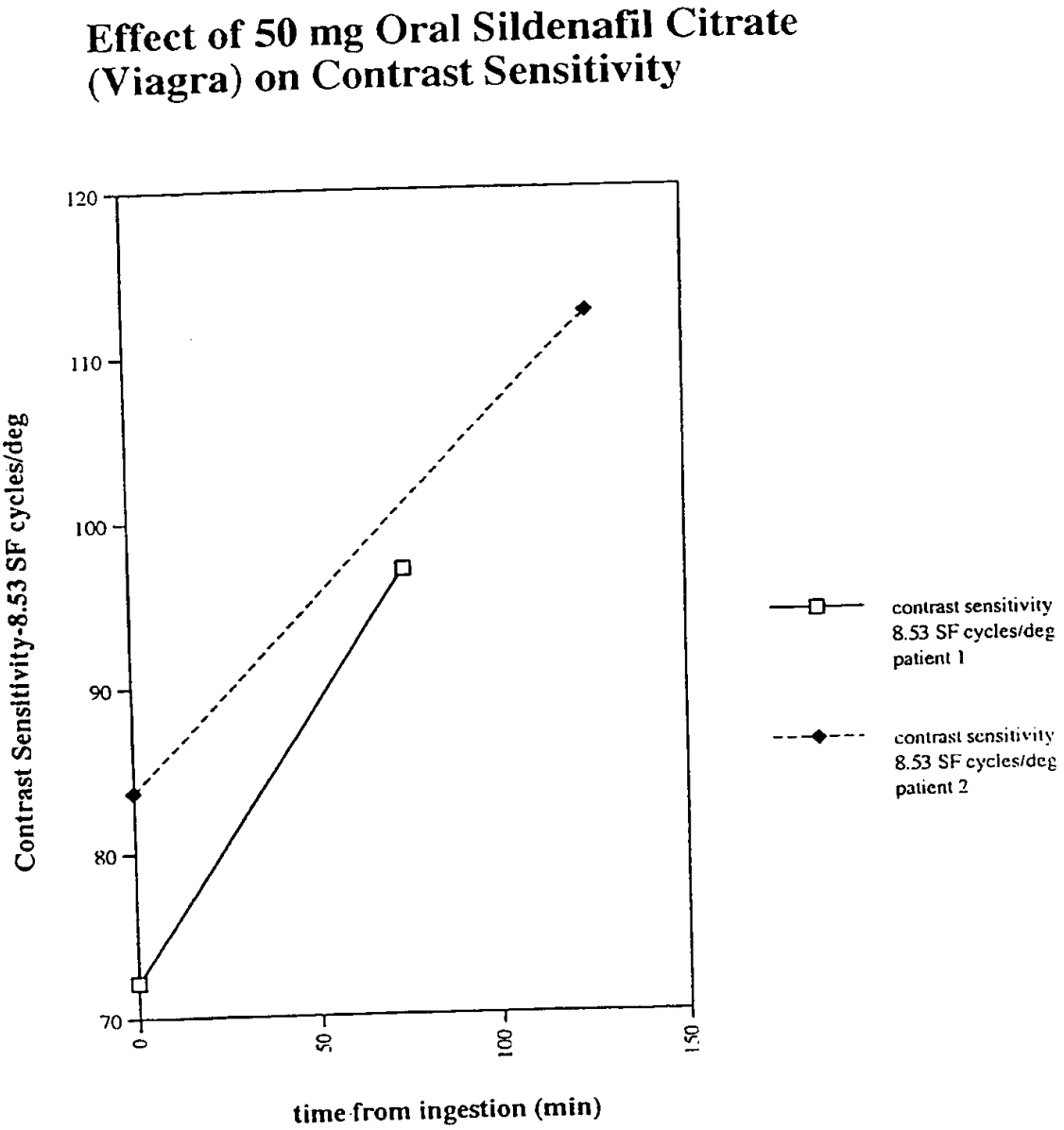

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Contrast Sensitivity
Contrast Sensitivity-8.53 SF cycles/deg
120
110
100
90
80
70
0
50
100
150
time from ingestion (min)
contrast sensitivity 8.53 SF cycles/deg patient 1
contrast sensitivity 8.53 SF cycles/deg patient 2

FIG. 2b

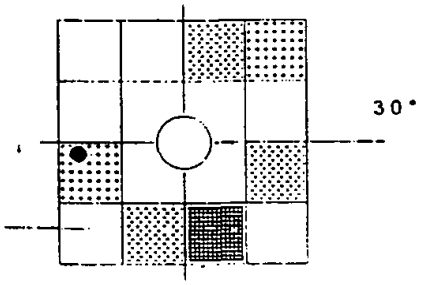
LEFT EYE

Test Duration: 04:58 min

Threshold (dB)

33	28	24	24	
26	30	29	29	
		29		
24	28	28	24	
27	24	20	31	

Deviation



MD -4.19 dB P < 5%
PSD +4.62 dB

FIXATION ERRS: 0/6
FALSE POS ERRS: 0/6
FALSE NEG ERRS: 0/3

Probability Symbols
- P >= 5%.
- P < 5%
- P < 2%
- P < 1%
- P < 0.5%

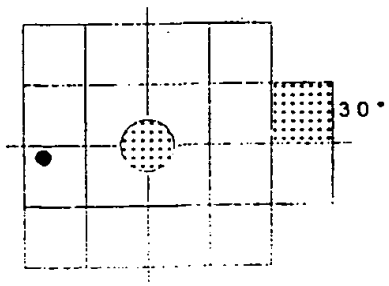
LEFT EYE

Test Duration: 05:43 min

Threshold (dB)

31	33	32	26	
27	30	56	34	23
		26		
28	45	32	29	30
56	28	28	33	

Deviation



MD +1.62 dB
PSD +13.65 dB P < 0.5%

FIXATION ERRS: 2/6
FALSE POS ERRS: 4/8
FALSE NEG ERRS: 0/5

Probability Symbols
- P >= 5%
- P < 5%
- P < 2%
- P < 1%
- P < 0.5%

FIG. 3a

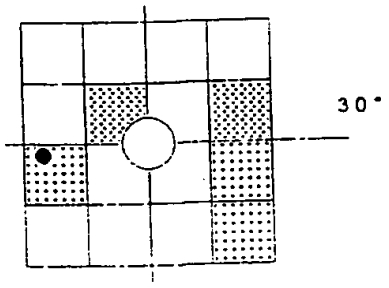
LEFT EYE

Test Duration: 04:43 min

Threshold (dB)

29	26	33	30
27	23	28	23
		29	
24	32	31	25
28	28	31	24

Deviation



MD -3.05 dB
PSD +4.48 dB

FIXATION ERRS: 0/6
FALSE POS ERRS: 0/6
FALSE NEG ERRS: 0/3

Probability Symbols
- P >= 5%
- P < 5%
- P < 2%
- P < 1%
- P < 0.5%

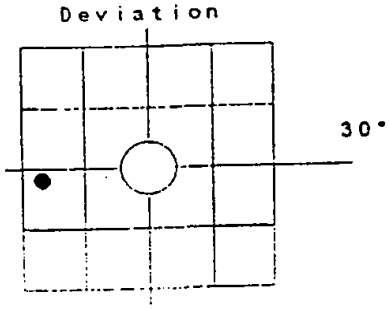
LEFT EYE

Test Duration: 04:46 min

Threshold (dB)

33	29	32	33
34	31	35	33
		29	
28	34	32	33
32	32	36	34

Deviation



MD -0.99 dB
PSD +3.30 dB

FIXATION ERRS: 0/6
FALSE POS ERRS: 0/6
FALSE NEG ERRS: 0/3

Probability Symbols
- P >= 5%
- P < 5%
- P < 2%
- P < 1%
- P < 0.5%

FIG. 3b

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Pulsatile Ocular Blood Flow

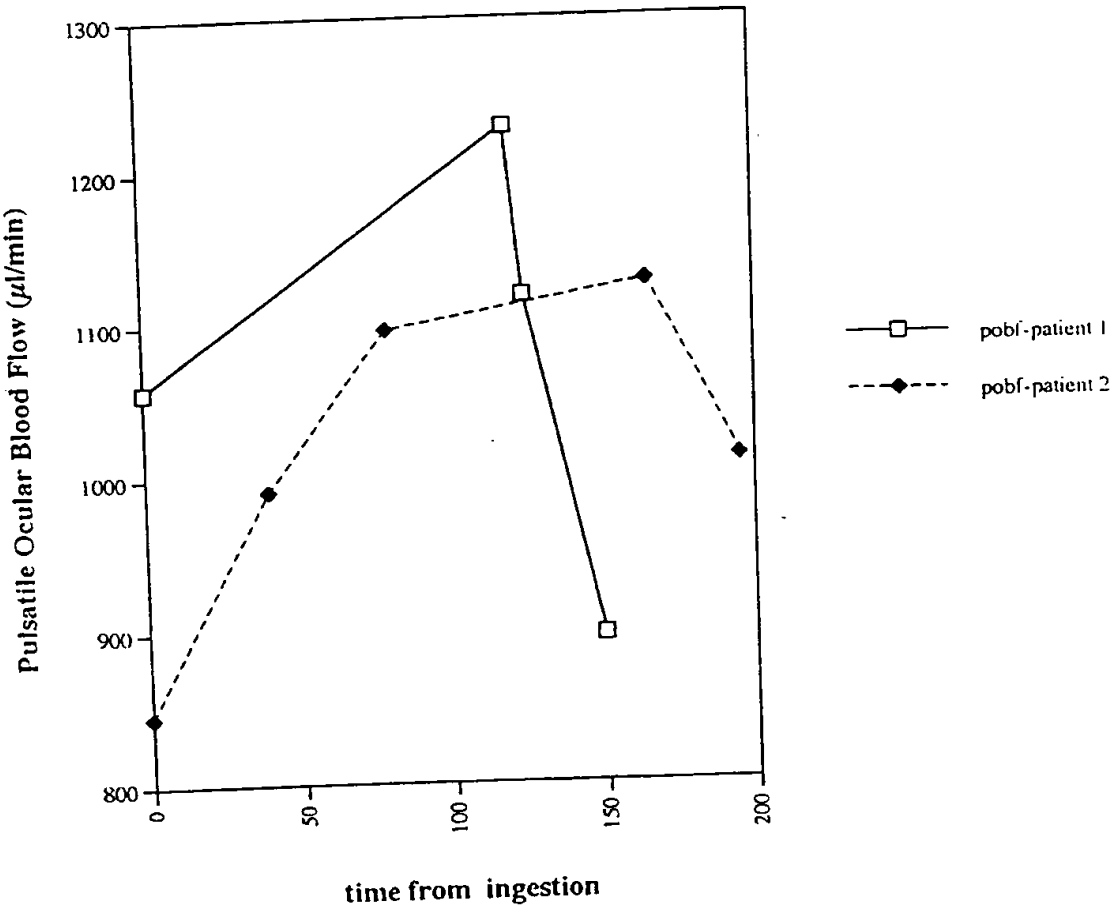


FIG. 4a

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Intraocular Pressure measured concomitantly with OBF

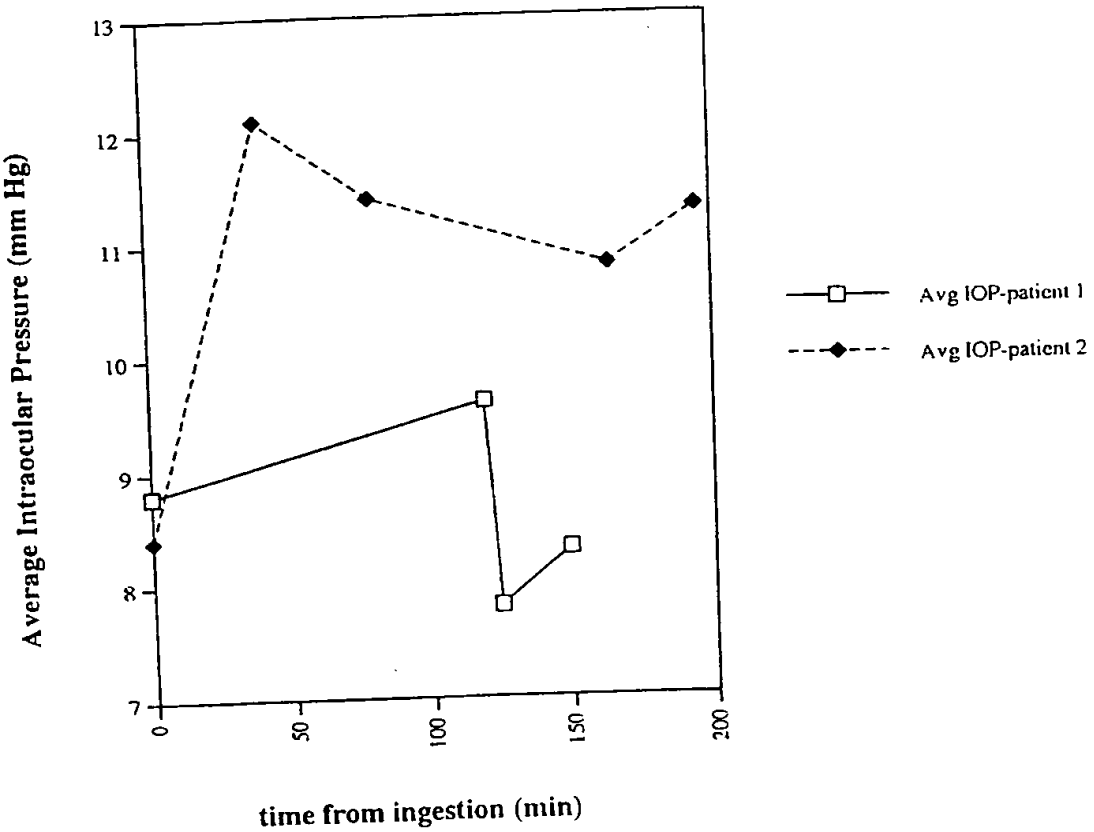


FIG. 4b

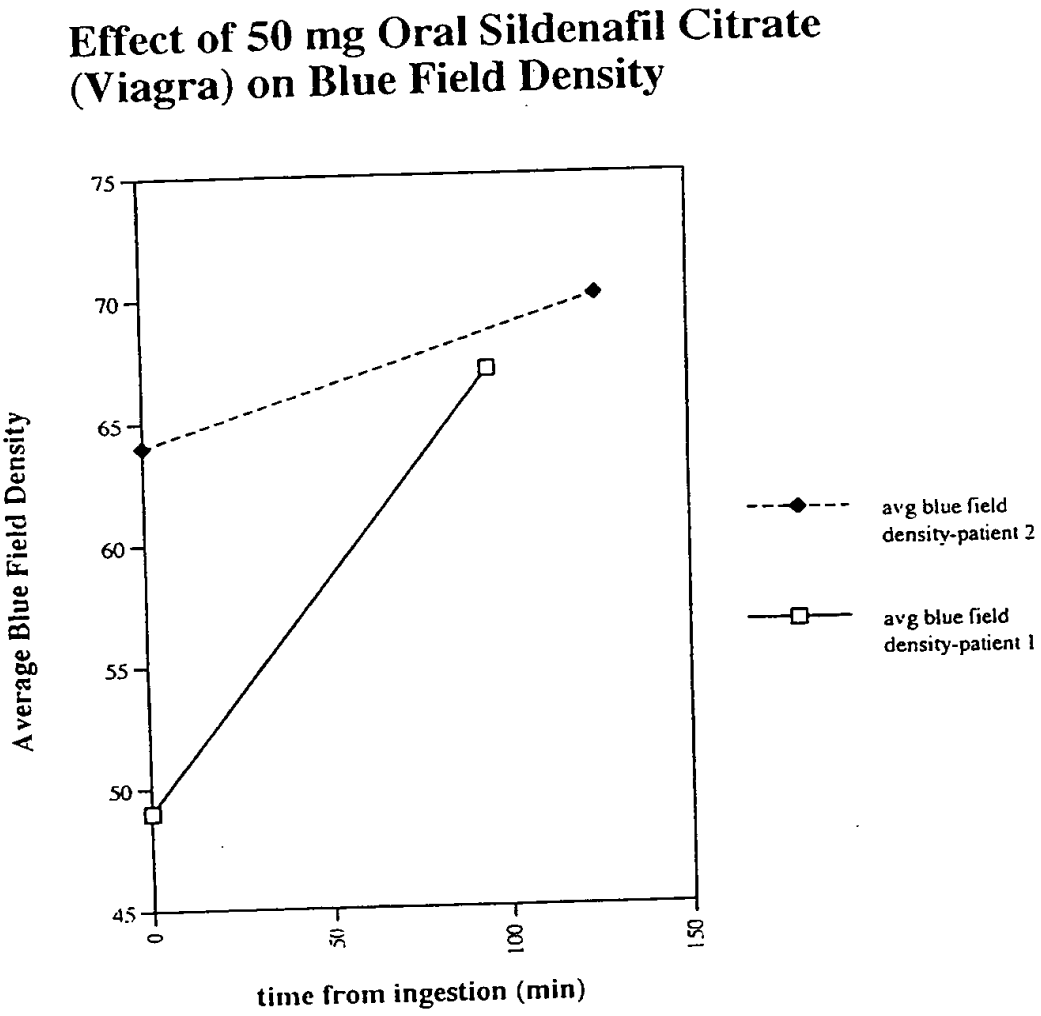

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Blue Field Density
Average Blue Field Density
75
70
65
60
55
50
45
0
50
100
150
time from ingestion (min)
avg blue field density-patient 2
avg blue field density-patient 1

FIG. 5a

Effect of 50 mg Oral Sildenafil Citrate (Viagra) on Blue Field Mean Velocity

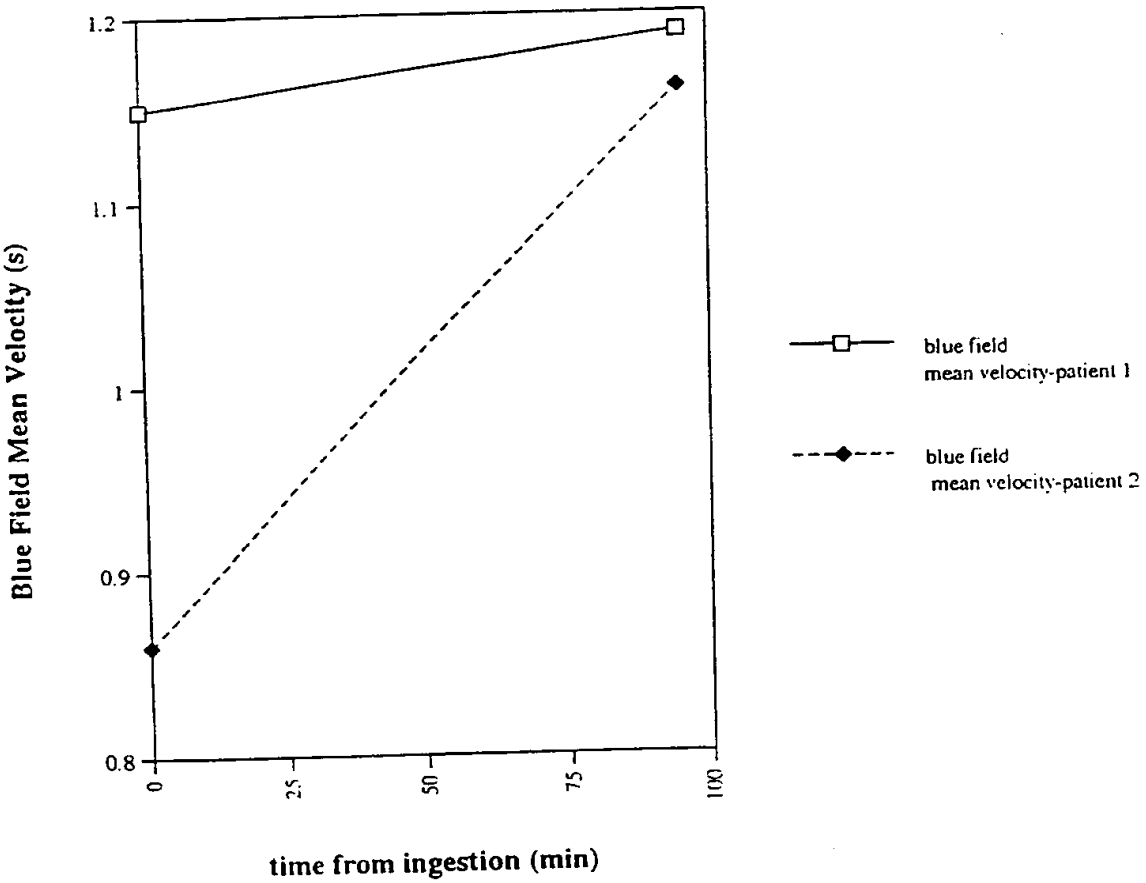


FIG. 5b

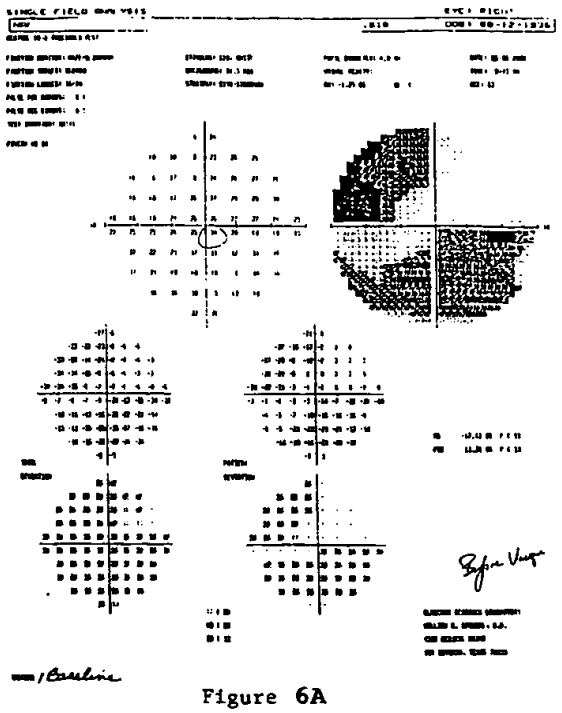


Figure 6A

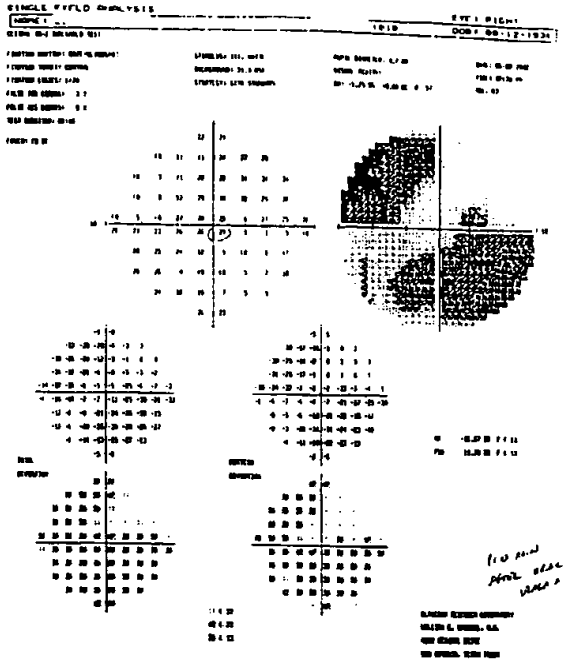


Figure 6B

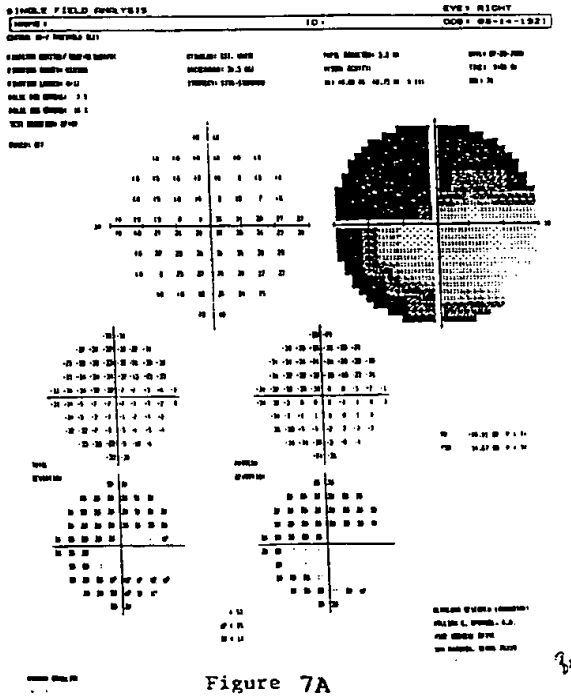


Figure 7A

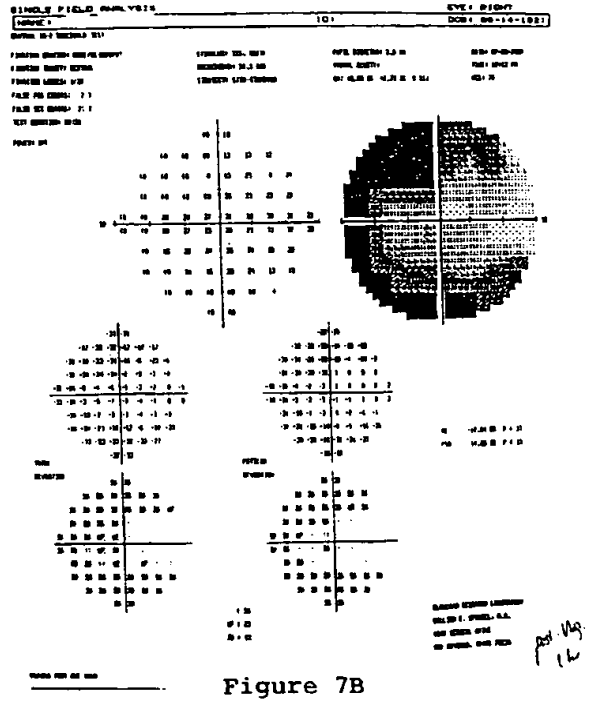


Figure 7B